UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: BENICAR (OLMESARTAN) PRODUCTS LIABILITY LITIGATION	MDL No. 2606 HON. ROBERT B. KUGLER
THIS DOCUMENT RELATES TO ALL CASES	

AFFIDAVIT OF STEPHEN M. LAGANA, M.D.

STATE OF NEW YORK:

COUNTY OF NEW YORK :

STEPHEN M. LAGANA, M.D., states as follows:

1. I am a physician retained as an expert witness in this litigation. This Affidavit is based upon my personal knowledge.

2. I have been provided the March 13, 2017 Memorandum Opinion and Order of the Court ("Order"). This Affidavit is submitted in response, as directed in the Order.

3. I have reviewed the parts of my deposition testimony referenced in the Court's Order. Respectfully, I did not testify that I "reviewed the charts of 16 patients who were exposed to olmesartan who were classified as having seronegative celiac disease." When I stated "we started in our hospital reviewing charts of patients," I was referring to the group of doctors I work with at the Celiac Center. The records were reviewed by other physicians, who had direct clinical involvement with the patients. As I next stated, "And my clinical colleagues uncovered a number of cases – I believe there were 16 cases – of patients who were exposed to olmesartan who were classified as having seronegative celiac disease." (24:7-26:14). The reference to 16

patients is a reference to a published study titled: Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma, Am J Gastroenterol 2013;108:647-653, authored by Columbia physicians. The senior author, and Guarantor of the article, is the senior clinician in the Celiac Center, Dr. Peter Green, who is the doctor who first advised us of the upcoming publication of the Mayo Clinic paper regarding olmesartan. I am not an author of the article. In that study, copy attached as Exhibit 1, the authors discussed 72 patients who had been diagnosed at Columbia with seronegative villous atrophy (meaning they had villous atrophy, which is characteristic of celiac disease, but were found to test negative on celiac serologies). The article states in part, on page 650: "**We identified 16 patients taking olmesartan**, of whom 68% had increased subepithelial collagen in addition to VA. Upon discontinuation of this medication, all 15 patients on whom we had follow up data improved symptomatically, no longer requiring immunosuppressive therapy if they had previously been on it (budesonide, prednisone, and azathioprine), and some have resumed a gluten-containing diet with no recurrence of symptoms. Notably, one patient who had symptomatic improvement off olmesartan was then rechallenged with the medication and symptoms recurred. The role of olmesartan and other angiotensin receptor blockers in enteropathy needs to be investigated further." I did not review the medical charts of the 16 patients referenced, that was done by some or all of the clinicians who authored the article, to the best of my knowledge. I was asked on page 32 of my deposition who was involved in contacting the 16 patients discussed in the article, and testified: "Well, we have a Celiac Disease Center with several physicians who deal with adults' complicated celiac disease, such as Dr. Peter Green, Dr. Benjamin Lebwohl, and Dr. Suzanne Lewis. So I would say that this was probably a center-wide effort and who was actually making the phone calls, I couldn't tell you." (32:8-19).

4. On page 126 line 16 to page 27 line 9 of my deposition, I testified that I saw "follow up biopsies of patients who had discontinued olmesartan on the basis of recommendations from Columbia physicians and the degree of improvement, striking, striking." This occurred in a clinical context, before I was ever contacted to be an expert in this litigation. I did not do so in connection with the writing of the report in this case, as it occurred years earlier. It was the review of biopsies showing improvement with discontinuation of olmesartan that I reference on page 27 as having, "contributed to my thinking and it seemed to me well beyond what you could imagine would be a chance association." I was not performing a retrospective chart review. Furthermore, as I was encountering these cases in clinical practice, I was not keeping a list of such patients. I then pointed out in my deposition: "And since then, I've followed the medical literature pretty closely. I read everything I see that relates to olmesartan enteropathy and I have over time certainly become more convinced that this drug does cause this syndrome in some patients." (27:10-17).

5. I understand that one issue is whether I have "possession, custody or control" of the medical records of the patients I was discussing in the deposition. I do not own, possess, or have custody or control of the medical records, as they are owned, maintained, and controlled by my employer, Columbia University. I do not have the right to redact or produce the medical records. I have confirmed this with the Columbia legal department.

6. I provided the Memorandum Opinion and Order to the Columbia legal department, and asked for written confirmation as to the ownership of the medical records and whether I have the right or ability to redact and produce the medical records. In response I was provided the letter attached to this Affidavit as Exhibit 2. Columbia has confirmed that I do not

own the medical records, I do not have possession, custody, or control, nor do I have the right to produce the medical records, redacted or not.

7. The medical records are maintained in the electronic records system of Columbia University, and are maintained by the medical records department. In order to obtain the reports of the biopsies that I reviewed, one would need to serve a subpoena on Columbia University, and request: "The pathology reports of patients of the Columbia Celiac Center, for biopsies reviewed by Dr. Stephen Lagana, for patients who stopped using Olmesartan, resulting in improvement in the histopathology." If Columbia permits me to do so, that request will enable me to review pathology reports, for production pursuant to the subpoena.

8. I am concerned about the request to produce the medical records of patients who are not plaintiffs in this litigation. I believe it is an invasion of patients' privacy, and is a distraction and burden for my employer, however I will comply and assist in the production of the medical records if requested to do so by my employer, Columbia, in response to a subpoena. Due to my concerns over patient privacy, and the involvement of and burden this is placing on my employer, if I had known when I was asked to act as an expert witness in this litigation that I would be subjected to an Order to produce the medical records of Columbia patients uninvolved in litigation, I would have declined to act as an expert. If medical records are to be produced, I request that they be redacted to remove all personal identification, including aspects of the records such as dates of procedures, dates of office visits, and social history, from which the patient would easily recognize himself or herself, and that an Order be entered limiting access to the heavily redacted medical records, only to those who would have to see the records.

STEPHEN M. LAGANA, M.D.

Sworn to and Subscribed
Before me this 28th Day
Of March, 2017.

Notary Public of the State of New York

PATRICIA SACHS CATAPANO
NOTARY PUBLIC, State of New York
No. 4691405
Qualified in Westchester County
Commission Expires Dec. 17, 20[illegible]

EXHIBIT

1

Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma

Marisa DeGaetani, MD[1,2], Christina A. Tennyson, MD[1,2], Benjamin Lebwohl, MD, MS[1,2], Suzanne K. Lewis, MD[1,2], Hussein Abu Daya, MD[1], Carolina Arguelles-Grande, MD[1], Govind Bhagat, MBBS[3] and Peter H.R. Green, MD[1,2]

OBJECTIVES: **Patients with villous atrophy (VA) and negative celiac disease (CD) serologies pose a diagnostic and therapeutic dilemma. When a definitive etiology for VA is not determined, patients are characterized as having unclassified sprue (US), the optimal management of which is unknown.**

METHODS: **We studied adult patients with VA on biopsy and negative celiac serologies, evaluated at our tertiary referral center over a 10-year period. Testing for HLA DQ2/8 alleles, antienterocyte antibodies, giardia stool antigen, bacterial overgrowth, total serum immunoglobulins, and HIV was noted. Treatment, response, and repeat-biopsy findings were recorded.**

RESULTS: **The most common diagnoses of the 72 patients were seronegative CD, medication-related villous atrophy, and US. Of those with US, the majority reported symptomatic improvement with immunosuppressive therapy. Some patients initially labeled as unclassified were found to have VA associated with olmesartan use.**

CONCLUSIONS: **The role of medications in the development of VA and the optimal dose and length of immunosuppression for patients with US should be investigated further.**

Am J Gastroenterol 2013;108:647–653; doi:10.1038/ajg.2013.45

Introduction

Celiac disease (CD) is an immune-mediated disorder occurring in people genetically susceptible to gluten and results in varying degrees of villous atrophy (VA), crypt hypertrophy, and an increase in intraepithelial lymphocytes (1,2). However, these biopsy findings are not specific for CD. The diagnosis of CD is supported by positive antibody testing (tissue transglutaminase, deamidated gliadin peptide, and antiendomysial antibodies) as well as symptomatic and histologic response to a gluten-free diet (GFD). Most with CD have positive celiac serologies, but not all. Lesser degrees of VA are more frequently seen in seronegative CD patients (3). Genetic testing for the HLA alleles DQ2 and/or DQ8 supports the diagnosis (2).

Although CD is the most common cause of VA (4), patients with VA and negative celiac serologies are encountered, posing a diagnostic and therapeutic dilemma. Possible etiologies associated with VA and absent celiac serologies include common variable immunodeficiency (CVID), autoimmune enteropathy, small intestinal bacterial overgrowth, infection, intestinal lymphoma, collagenous sprue, Crohn's disease, and tropical sprue. VA can also result from certain medications. When celiac serologies are negative on a gluten-containing diet, alternative etiologies for VA should be considered before diagnosis of seronegative CD, to prevent an unnecessary lifelong GFD (5). At times, no definitive etiology for VA can be determined, and the patient is labeled as having unclassified sprue (US).

We analyzed our prospectively maintained Celiac Disease Center database to identify patients with seronegative VA. In addition to describing the various etiologies of seronegative VA, we also examined the response to treatment.

Methods

We report a series of adult patients with seronegative VA evaluated over a 10-year period (from 2001 to 2011) at a tertiary-care referral center. Patients included in this study were those with VA on duodenal

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biopsy and negative celiac serology (including tissue transglutaminase (TTG), deamidated gliadin peptide (DGP), and antiendomysial antibodies). Data regarding demographics, concomitant autoimmune disease, family history of CD, and initial biopsy results were collected. Testing was performed for human leukocyte antigen (HLA) DQ2/8 alleles, antienterocyte antibodies, giardia stool antigen, bacterial overgrowth, HIV, serum immunoglobulins, and T-cell receptor gene rearrangement. We sought the use of specific medications that have been involved with the development of VA, including mycophenolate mofetil and methotrexate; in light of the recently published case series from the Mayo Clinic describing an association between olmesartan and a sprue-like syndrome (6), we also identified patients taking this medication. Treatment, response, and repeat-biopsy results were recorded.

Patients in this study were considered to have seronegative CD if they had negative TTG, DGP, and antiendomysial antibody tests, positive genetic tests for CD, biopsy findings that were consistent with a diagnosis of CD (most notably intraepithelial lymphocytosis together with VA, which has been shown to be a sensitive marker for CD (7)), and response to a GFD (symptomatically and/or histologically), and tested negative for other etiologies of VA. As prior studies have demonstrated that the use of a single antibody test can underdiagnose CD (8,9), detection of more than one negative antibody test was looked for before a patient was labeled with seronegative CD.

Characteristic features used to diagnose patients with other etiologies of seronegative VA are as follows: CVID required decreased serum levels of at least two immunoglobulin subtypes in the setting of a normal albumin level, supported by biopsy findings consistent with CVID, including decreased plasma cells in the lamina propria. All patients with a diagnosis of giardiasis had positive giardia stool testing and responded symptomatically and/or histologically to treatment with metronidazole. Small intestinal bacterial overgrowth was diagnosed with positive hydrogen breath testing and symptomatic/histologic response to antibiotics. Medication-related VA was diagnosed after improvement in symptoms and/or histology once a medication reported to cause VA was discontinued. Diagnosis of collagenous sprue required a thickened subepithelial collagen band on histology. In the diagnosis of autoimmune enteropathy, we looked for a strong history of autoimmune disease and gut autoantibodies, supported by biopsy findings characteristic of this diagnosis, including increased plasma cells in the lamina propria, decreased goblet cells, and lack of increased intraepithelial lymphocytes. Patients with tropical sprue had traveled to an endemic area, had low B12 levels, and improved with antibiotics. A diagnosis of lymphoma required a monoclonal population of T cells. Patients were labeled with unclassified sprue (US) if they had no clear unifying diagnosis to account for their VA. Clinical response was defined as resolution of symptoms. Histologic response was defined as improvement in the degree of VA on duodenal biopsy.

This study was approved by our institutional review board.

Table 1. Demographics of patients with seronegative villous atrophy

Total *N*	72
Female (*N*, %)	37 (51.4%)
Mean age (years)	59 (range 29–85)
Presented with diarrhea (*N*, %)	55 (76.4%)
Mean time of follow-up (months)	26.4

Results

A total of 72 patients were identified with seronegative VA. All patients had been referred with a diagnosis of poorly responsive/refractory CD. Demographic information is provided in **Table 1**. Final diagnoses included: seronegative CD, 20 (28%); medication-related VA, 19 (26%); US, 10 (14%); CVID, 4 (6%); autoimmune enteropathy, 3 (4%); giardia, 3 (4%); $CD4^+$ small intestinal T-cell lymphoma, 3 (4%); tropical sprue, 3 (4%); bacterial overgrowth, 2 (3%); collagenous sprue, 2 (3%); enteropathy-associated T-cell lymphoma, 1 (1%); Crohn's disease, 1 (1%); and extensive gastric metaplasia, 1 (1%) (**Figure 1** and **Tables 2–5**).

The mean follow-up for all patients was 26.4 months. Two patients died of unrelated causes, two died of complications of their disease (intestinal failure related to extensive gastric metaplasia and transformation of $CD4^+$ small intestinal T-cell lymphoma to an aggressive form), and two developed lymphoproliferative disorders (multiple myeloma and B-cell lymphoma).

Seronegative CD was the most common diagnosis in our study, seen in 20 of 72 patients (28%). This was followed by medication-related VA, largely as a result of olmesartan use (16 of 19 patients in this category). The other culprit medications were mycophenolate mofetil (2 patients)

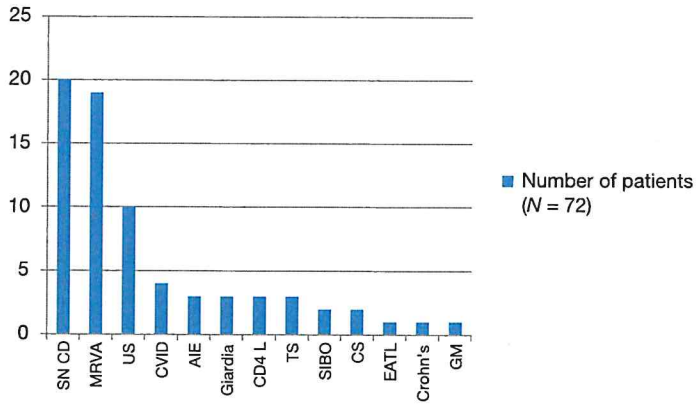

Figure 1. Etiologies of seronegative villous atrophy. AIE, autoimmune enteropathy; CD4 L, $CD4^+$ T-cell lymphoma; CS, collagenous sprue; CVID, common variable immunodeficiency; EATL, enteropathy-associated T-cell lymphoma; GM, gastric metaplasia; MRVA, medication-related villous atrophy; SIBO, small intestinal bacterial overgrowth; SN CD, seronegative celiac disease; TS, tropical sprue; US, unclassified sprue.

Table 2. Seronegative celiac disease

No.	Age (y)/sex	Fam Hx CD	AI dz	SIBO?	Culprit meds	Ig defic.	Giardia	A-E Ab	HLA DQ2/8	TCR	Degree VA initial bx	Clinical improv./ GFD	Degree of VA f/u biopsy	F/u bx improv.?	Required immuno-suppression	F/u time after initial visit (mo.)
1	59/M	–	–	NT	–	–	–	–	+	NT	PVA	+	NA	NA	–	12
2	36/F	–	–	NT	–	–	–	NT	NT	+ Clonal	DNS	+	Normal	+	–	22
3	55/F	+	–	NT	–	–	NT	NT	+	NT	PVA	+	NA	NA	–	72
4	44/M	+	+	NT	–	–	NT	NT	+	NT	PVA	+	Normal	+	–	36
5	48/F	–	+	+	–	–	–	NT	NT	–	TVA	+	PVA	+	–	60
6	43/F	–	–	NT	–	–	–	NT	+	NT	PVA	+	Normal	+	–	36
7	33/M	+	–	NT	–	–	NT	NT	+	NT	STVA	+	NA	NA	–	96
8	42/M	–	–	NT	–	IgM	NT	NT	+	–	PVA	+	Normal	+	–	12
9	72/M	–	–	NT	–	–	NT	–	+	NT	PVA	+	NA	NA	–	4
10	29/M	–	–	NT	–	–	NT	–	NT	NT	STVA	+	NA	NA	–	5
11	72/M	–	–	NT	–	–	–	Weak +	+	NT	TVA	+	NA	NA	–	10
12	40/F	–	–	+[a]	–	–	NT	NT	+	NT	PVA	+	NA	NA	–	24
13	64/M	–	–	NT	–	–	NT	NT	+	NT	PVA	+	NA	NA	–	12
14	67/F	–	+	+[a]	–	IgM	–	NT	+	NT	TVA	+	Normal	+	–	12
15	58/M	–	–	NT	–	–	–	NT	NT	NT	PVA	+	NA	NA	–	3
16	70/M	–	–	NT	–	–	NT	–	+	–	DNS	+	NA	NA	+	6
17	60/F	+	–	NT	–	–	NT	–	+	–	PVA	+	NA	NA	+	108
18	70/M	–	–	–	–	IgM	NT	NT	NT	NT	STVA	+	Normal	+	+	24
19	62/F	–	–	+	–	IgM	NT	NT	+	–	STVA	+	PVA	+	+	36
20	47/F	–	–	–	–	IgM	–	–	+	–	DNS	+	NA	NA	+	5

A-E Ab, anti-enterocyte antibody; AI dz, autoimmune disease; bx, biopsy; CD, celiac disease; defic., deficiency; DNS, degree of villous atrophy was not specified; Fam Hx, family history; f/u, follow-up; GFD, gluten-free diet; HLA DQ2/8, human leukocyte antigen DQ2/8 alleles; improv., improvement; NA, not applicable; No., patient number; NT, not tested; PVA, partial villous atrophy; SIBO, small intestinal bacterial overgrowth; STVA, subtotal villous atrophy; TCR, T-cell receptor; TVA, total villous atrophy; VA, villous atrophy.
[a]Remote history of treated small intestinal bacterial overgrowth.

Table 3. Medication-related villous atrophy

No.	Age (y)/sex	HLA DQ2/8	Culprit meds?	Degree VA initial bx	Increase subepithelial collagen	Increase IEL on bx	GFD	Clinical improv./ GFD	Abx	Clinical improv./ Abx	IS	Clinical improv./ IS	Relapse off IS?	Clinical improv. after stopping med	Bx improv. after stopping med	F/u time (mo.)
1	61/M	+	Olmesartan	TVA	+	+	+	–	+	?	+	+	+	+	NA	24
2	73/F	+	Olmesartan	TVA	+	+	+	–	–	NA	+	+	+	+	NA	21
3	82/M	NT	Olmesartan	PVA	+	+	+	–	+	?	+	+	+	+	NA	66
4	63/M	+	Olmesartan	STVA	+	+	+	–	–	NA	+	+	+	+	NA	50
5	69/F	–	Olmesartan	TVA	+	+	+	–	–	NA	+	+	+	+	+	12
6	66/M	+	Olmesartan	TVA	+	+	+	–	+	+	+	+	+	+	+	12
7	75/F	+	Olmesartan	DNS	+	+	+	–	+	+	+	+	+	?	NA	6
8	63/F	+	Olmesartan	TVA	+	+	+	–	–	NA	+	+	+	+	NA	42
9	52/M	NT	Olmesartan	STVA	–	–	+	–	+	–	+	+	+	+	NA	18
10	58/F	+	Olmesartan	PVA	+	–	+	–	–	NA	+	+	+	+	NA	24
11	83/M	+	Olmesartan	DNS	–	+	+	–	+	–	+	+	+	+	NA	11
12	67/F	+	Olmesartan	PVA	+	–	+	–	+	–	+	+	+	+	NA	8
13	75/M	+	Olmesartan	TVA	–	–	+	+	–	NA	+	+	+	+	NA	21
14	68/F	+	Olmesartan	TVA	–	+	+	–	+	–	+	+	+	+	NA	36
15	62/M	+	Olmesartan	TVA	+	+	+	–	+	–	+	+	+	+	NA	10
16	64/F	NT	Olmesartan	DNS	–	–	+	–	–	NA	+	+	+	+	NA	12
17	74/F	+	MMF	PVA	+	–	+	–	–	NA	NA	NA[a]	NA	+	NA	7
18	57/F	NT	MMF	PVA	–	–	–	NA	–	NA	NA	NA[a]	NA	+	NA	3
19	67/F	NT	Methotrexate	PVA	–	–	+	+	–	NA	NA	NA[a]	NA	+	+	120

Abx, antibiotics; bx, biopsy; f/u, follow-up; GFD, gluten-free diet; HLA DQ2/8, human leukocyte antigen DQ2/8 alleles; IEL, intraepithelial lymphocytes; improv., improvement; IS, immunosuppression; MMF, mycophenolate mofetil; NA, not applicable; No., patient number; NT, not tested; PVA, partial villous atrophy; STVA, subtotal villous atrophy; TVA, total villous atrophy; VA, villous atrophy.
[a]Culprit meds were immunosuppressive agents.

and methotrexate (1 patient). Twelve of the patients with medication-related VA had biopsies consistent with collagenous sprue (11 olmesartan and 1 mycophenolate). US was seen in 10 of 72 patients (14%); 70% were female, and the mean age was 62 years (range 33–82). All US patients were symptomatic at presentation, diarrhea being the main complaint in 70%. Three patients had a history of autoimmune diseases, none had a family member with CD, and 70% were positive for HLA DQ2/8. Initial biopsy revealed partial villous atrophy in 4 of 10 patients, subtotal villous atrophy in 1 of 10, and total villous atrophy in 4 of 10. The degree of VA was not specified in 1 patient. Increased intraepithelial lymphocytes were seen in 90% of patients. The results of additional diagnostic studies are shown in **Table 5**. One patient (patient 8) subsequently developed a low-grade B-cell lymphoma in the bone marrow with no evidence of small intestinal involvement.

Eight patients with US were tried on a GFD, but only 2 patients (25%) experienced initial symptomatic improvement. One patient showed no histologic improvement on repeat biopsy, and the other showed some degree of histologic improvement; however, repeat biopsy was performed only after immunosuppressive therapy was started. Response to a GFD is not a good predictive factor for CD, as it has not been shown to be a specific test for CD (10,11). Six patients were treated with antibiotics, and one reported improvement in symptoms (patient 9). She was treated with rifaximin for 10 days and experienced temporary improvement of her diarrhea. Notably, the VA on her repeat biopsy had improved before antibiotic therapy, but histology remained abnormal. Eighty percent received immunosuppressive agents, and 86% of these showed symptomatic improvement in follow-up data. Medications included budesonide, beclomethasone, prednisone, azathioprine, and 6-mercaptopurine. Of these patients, all experienced improved symptoms within 2 months. Only one patient (patient 5) was able to successfully stop treatment after 4 months of therapy. One patient (patient 1) had no response to any treatment, and one patient was lost to follow-up after immunosuppressive therapy was started.

Discussion

Seronegative VA is uncommon; however, it is important to be able to differentiate between seronegative CD and other causes of VA, as their prognosis and treatment are distinct, despite their often having similar clinical presentations and biopsy findings. Of the 72 patients seen over a 10-year period at our single tertiary-care referral center, we found a definitive etiology for seronegative VA in approximately 85%. An interesting finding in our series was the number of patients who were initially labeled with unclassified sprue who were ultimately found to have VA as a result of olmesartan use.

The most common diagnosis seen in our series was seronegative CD. Antibody testing using TTG IgA and endomysial IgA is highly sensitive and specific for CD, whereas antigliadin antibody testing is not (13–15). The newer DGP assay is also highly sensitive and specific for CD and has been shown to detect patients who were seronegative by TTG testing (16); however, only one of the patients with seronegative CD in our study was tested for antibodies to DGP. Even in IgA deficiency, most patients can still mount an IgG antibody response to TTG and gliadin (17,18). However, in the presence of partial VA or silent or subclinical CD, antibody testing may be negative (3,19). Our seronegative CD patients all had histologic findings and responded symptomatically to treatment with a GFD, and all eight who underwent repeat biopsy at the time of clinical improvement had improved histology.

The second largest group comprised those with VA from medication use. Specific medications, including methotrexate, mycophenolate mofetil, and azathioprine, have been considered to cause VA (20–24), as well as the angiotensin receptor blocker olmesartan, as reported in 22 patients from the Mayo Clinic (6). These authors also reported an association between olmesartan and collagenous sprue (25). We identified 16 patients taking olmesartan, of whom 68% had increased subepithelial collagen in addition to VA. Upon discontinuation of this medication, all 15 patients on whom we had follow-up data improved symptomatically, no longer requiring immunosuppressive therapy if they had previously been on it (budesonide, prednisone, and azathioprine), and some have resumed a gluten-containing diet with no recurrence of symptoms. Notably, one patient who had symptomatic improvement off olmesartan was then rechallenged with the medication and symptoms recurred. The role of olmesartan and other angiotensin receptor blockers in enteropathy needs to be investigated further.

Unclassified sprue (US), a diagnosis of exclusion, was seen in 14% of our patients. Although this result is lower than that reported by Pallav *et al.*, who diagnosed unspecified enteropathy in 10 of 30 of their patients with seronegative VA (10), before identifying olmesartan as a cause of VA, we too had considered 30% of our seronegative patients to have US. Patients with US all lacked an alternate single unifying diagnosis; however, HLA DQ2/8 alleles were found in 70% of those tested. Most patients responded to treatment with immunosuppressive therapy. In our study, only one patient had an isolated deficiency of serum IgG as in the series of Pallav *et al.* (10). Yet two US patients had isolated low levels of IgM, and 12 patients with a known etiology for their VA had an isolated IgM deficiency. The significance of detecting low IgM levels in patients presenting with sprue-like disease is unclear (26), though an association between IgM deficiency and CD has been reported (27).

Although eight patients were found to have small intestinal bacterial overgrowth by breath testing at the time of evaluation for their VA, in only two was it considered to be the sole cause of their VA. One patient with total VA was found to have enteropathy-associated T-cell lymphoma, a large-cell high-grade non-Hodgkin's lymphoma (28), responsible for the VA without evidence of CD. Additionally, we identified three patients who were referred for poorly responsive CD and found to have VA due to an intestinal lymphoma that primarily involved the lamina propria, which was distended by an infiltrate of small-sized $CD4^+$ T cells. This is a rare type of primary intestinal T-cell lymphoma, with only a few reported cases describing prolonged survival, which can histologically mimic but is not associated with CD (29).

Table 4. Other causes of villous atrophy

Diagnosis	Age (y)/ sex	Fam Hx of CD	AI dz	SIBO?	Culprit meds?	Ig defic.	Giardia	A-E Ab	HLA DQ2/8	TCR	Degree VA initial bx	GFD	Clinical improv/ GFD	Abx	Clinical improv/ Abx	IS	Clinical improv/ IS	Degree VA f/u bx	F/u bx improv?	F/u time (mo.)
CVID	45/F	–	–	+	–	IgA, IgG, IgM	–	NT	+	–	DNS	+	–	+	+	+	?	PVA	–	3
CVID[a]	60/M	–	–	NT	–	IgA, IgG, IgM	+	NT	+	–	DNS	+	–	+	+	–	NA	Normal	+	12
CVID	73/M	–	–	NT	–	IgG, IgM	–	–	+	–	PVA	+	–	–	NA	+	+	PVA	–	30
CVID	29/F	+	+	NT	–	IgA, IgG, IgM	–	–	+	NT	PVA	–	NA	–	NA	+	+	NA	NA	6
AIE	66/F	–	–	NT	–	–	NT	+	–	NT	PVA	–	NA	–	NA	–	NA	NA	NA	5
AIE	59/M	–	–	NT	–	–	–	+	+	–	TVA	+	–	–	NA	+	+	TVA	–	12
AIE	59/M	+	–	NT	–	IgM	–[b]	–	+	NT	PVA	–	NA	+	+	+	+	NA	NA	6
Giardia	54/M	–	–	–	–	–	+	–	+	–	TVA	+	–	+	+	–	NA	Normal	+	12
Giardia	41/M	–	–	NT	–	–	+	NT	–	NT	TVA	+	–	+	+	–	NA	STVA	+	2
Giardia	32/M	–	–	–	–	–	+	NT	NT	NT	PVA	+	–	+	+	–	NA	Normal	+	60
CD4 lymphoma	51/F	+	–	–	–	–	NT	–	–	+ Clonal	STVA	+	–	–	NA	+	+	STVA	–	3
CD4 lymphoma	46/M	–	–	–	–	–	–	NT	+	+ Clonal	TVA	+	–	+	–	+	+	TVA	–	144
CD4 lymphoma	70/M	–	–	–	–	–	–	NT	+	+ Clonal	STVA	+	–	–	NA	+	+	STVA	–	30
SIBO	50/F	–	–	+	–	–	–	NT	+	NT	PVA	+	–	+	+	–	NA	Normal	+	1
SIBO	70/F	–	–	+	–	–	–	NT	–	–	TVA	+	–	+	+	+	+	Normal	+	84
Tropical sprue	72/M	–	–	NT	–	IgM	–	NT	+	–	PVA	–	NA	+	+	–	NA	PVA	–	16
Tropical sprue	40/F	–	–	NT	–	–	–	NT	+	NT	PVA	+	–	+	+	–	NA	NA	NA	6
Tropical sprue	85/F	–	–	NT	–	–	–	–	+	–	STVA	+	–	+	+	+	–	STVA[c]	–	12
Collagenous sprue	34/F	+	–	NT	–	–	NT	NT	NT	–	TVA	+	+	+	?	+	+	PVA	+	36
Collagenous sprue	63/M	+	+	NT	–	–	NT	–	NT	+ Clonal	TVA	+	+	–	NA	+	+	TVA	–	12
T-cell lymphoma	50/M	–	–	NT	–	–	NT	NT	+	+ Clonal	DNS	+	–	+	+	–	NA	NA	NA	12
Gastric metaplasia	68/F	–	+	NT	Methotrexate	IgM	–	NT	+	NT	TVA	+	–	+	–	+	–	TVA	–	12
Crohn's disease	76/M	–	+	NT	–	–	–	–	+	–	PVA	+	–	–	NA	+	?	Normal	+	72

Abx, antibiotics; A-E Ab, anti-enterocyte antibody; AI dz, autoimmune disease; AIE, autoimmune enteropathy; bx, biopsy; CD, celiac disease; CVID, common variable immunodeficiency; defic., deficiency; DNS, degree of villous atrophy was not specified; Fam Hx, family history; f/u, follow-up; GFD, gluten-free diet; HLA DQ2/8, human leukocyte antigen DQ2/8 alleles; improv., improvement; IS, immunosuppression; NA, not applicable; NT, not tested; PVA, partial villous atrophy; SIBO, small intestinal bacterial overgrowth; STVA, subtotal villous atrophy; TCR, T-cell receptor; TVA, total villous atrophy; VA, villous atrophy.
[a]Although the patient had positive giardia testing and improved with antibiotics, the initial biopsy had findings consistent with autoimmune enteropathy, and so he was labeled as such, although it is likely that two processes were contributing to his presentation.
[b]Patient had biopsy consistent with autoimmune enteropathy.
[c]Biopsy done after immunosuppressive therapy but before antibiotic therapy.

To our knowledge, our series of seronegative VA is the largest study to date. However, given that our population was composed of referrals made to a tertiary-care center, it may not be an accurate representation of seronegative VA in general, which may contain a higher proportion of seronegative CD that is responsive to a GFD. Additionally, as the patients were seen by four different physicians over a 10-year period, different patterns of testing for the work-up of

Table 5. Unclassified sprue

No.	Age (y)/sex	Fam Hx of CD	AI dz	SIBO	Culprit meds	Ig defi-ciency	Giar-dia	A-E Ab	HLA DQ2/8	TCR	Degree VA initial bx	IEL on bx	GFD	Clinical improv./ GFD	Abx	Clinical improv./ Abx	IS	Clinical improv./ IS	Degree VA f/u bx	F/u bx im-prov.?	F/u time (mo.)
1	82/F	–	–	+	–	–	–	–	–	–	DNS	+	+	–	+	–	+	–	PVA	–	6
2	65/M	–	–	NT	–	IgM	NT	NT	+	NT	TVA	+	–	NA	+	–	+	+	NA	NA	1
3	67/F	–	–	+	–	–	–	Weak +	+	–	TVA	+	+	–	+	–	+	+	TVA	–	4
4	40/M	–	–	+	–	–	–	–	+	–	STVA	+	+	–	+	–	+	+	NA	NA	1
5	79/F	–	–	NT	–	IgG	–	NT	+	–	TVA	+	+	+	–	NA	+	+	STVA	+	6
6	78/M	–	+	NT	–	–	NT	–	+	–	TVA	–	+	–	–	NA	+	+	N/A	NA	1
7	62/F	–	–	–	–	IgA	NT	–	–	–	PVA	+	–	NA	+	–	+	?	PVA	–	2
8	65/F	–	+	–	–	IgA	–	–	+	–	PVA	+	+	–	–	NA	+	+	PVA	–	36
9	33/F	–	–	NT	–	–	–	NT	+	+ Clonal	PVA	+	+	–	+	+	–	NA	Nor-mal[a]	+	24
10	49/F	–	+	–	–	IgM	–	NT	–	NT	PVA	+	+	+	–	NA	–	NA	PVA	–	132

Abx, antibiotics; A-E Ab, anti-enterocyte antibody; AI dz, autoimmune disease; bx, biopsy; CD, celiac disease; DNS, degree of villous atrophy was not specified; Fam Hx, family history; f/u, follow-up; GFD, gluten-free diet; HLA DQ2/8, human leukocyte antigen DQ2/8 alleles; IEL, intraepithelial lymphocytes; improv., improvement; IS, immunosuppression; NA, not applicable; No., patient number; NT, not tested; PVA, partial villous atrophy; SIBO, small intestinal bacterial overgrowth; STVA, subtotal villous atrophy; TCR, T-cell receptor; TVA, total villous atrophy; VA, villous atrophy.
[a]Biopsy before antibiotic therapy started.

seronegative VA were noted. One area of testing that was poor was testing for HIV. Ideally, in all cases clinical response needs to be confirmed by histologic improvement on scheduled follow-up biopsies; however, we could not document this in all cases, as some patients were lost to follow-up or did not wish to undergo repeat biopsy.

Proposed work-up for seronegative VA. On the basis of our results, we propose that all patients with seronegative VA should initially be tested for HLA DQ2 and DQ8. If the test is negative, we would usually exclude CD. Immunoglobulin deficiency should also be excluded, both selective IgA deficiency and CVID. A thorough history should be obtained, which should include medication and travel history. We recommend further testing for antienterocyte antibodies, giardia antigen in the stool, and HIV, and breath testing for small intestinal bacterial overgrowth. If there is suspicion of lymphoma based on the pathological appearance, further studies including immunohistochemistry and testing for T-cell receptor gene rearrangement to identify occult lymphomas can be performed. Previous and initial biopsies should be obtained and reviewed by an experienced gastrointestinal pathologist in order to elucidate a potential etiology based on certain biopsy characteristics, for example, occult lymphoma and eosinophilic enteritis. If no clear etiology can be determined, and a patient is believed to have US, we recommend treatment based on the severity of the patient's illness—initially corticosteroids, such as budesonide and/or prednisone, with other immunosuppressive agents if necessary. The best agent, as well as the optimal treatment time, is unknown and needs to be researched further; however, our experience with budesonide would favor it as a first-line therapy (30). Patients with medication-related VA typically require immunosuppressive treatment for a period of time.

VA with negative celiac serology is uncommon. While most patients with seronegative VA in our study had either CD or other identifiable disease processes, some patients had VA of unclear etiology (US) that did not respond to a GFD alone and required immunosuppression.

CONFLICT OF INTEREST

Guarantor of the article: Peter H.R. Green, MD.

Specific author contributions: Marisa DeGaetani: acquisition of data, analysis and interpretation of data, drafting of the manuscript; Christina A. Tennyson, Benjamin Lebwohl, and Suzanne K. Lewis: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content; Hussein Abu Daya and Carolina Arguelles-Grande: acquisition of data, critical revision of the manuscript for important intellectual content; Govind Bhagat: study concept and design, critical revision of the manuscript for important intellectual content; Peter H.R. Green: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

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EXHIBIT

2

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March 23, 2017

By E-mail

To: Stephen M. Lagana, M.D.
Benjamin Lebwohl, M.D.

Subject: In Re: Benica (Olmesartan) Products Liability Litigation

Thank you for bringing the Court Order in this matter to my attention. As I told you, Columbia University owns the patient medical records which you create and review in your role as a clinical faculty member. You do not have custody, possession or control of these records, and Columbia does not agree that you may produce these records to the Court.

Patricia Sachs Catapano
Associate General Counsel

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